

[54] **2,2-DIFLUORO-TRANS-4,5,13,14-TETRAHYDRO-PGI₁ COMPOUNDS**

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[73] **Assignee:** The Upjohn Company, Kalamazoo, Mich.

[21] **Appl. No.:** 915,349

[22] **Filed:** Jun. 14, 1978

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 821,536, Aug. 3, 1977.

[51] **Int. Cl.²** C07D 307/93

[52] **U.S. Cl.** 260/346.73; 260/346.22; 542/426

[58] **Field of Search** 260/346.22, 346.73; 542/426

[56] **References Cited**
PUBLICATIONS

Fried et al., Proc. Natl. Acad. Sci. 74, 2199, 1977.

Primary Examiner—Henry R. Jiles

Assistant Examiner—Bernard Dentz

Attorney, Agent, or Firm—Robert A. Armitage

[57] **ABSTRACT**

The present invention relates to certain structural and pharmacological analogs of prostacyclin (PGI₂) which are 2,2-difluoro-trans-4,5,13,14-tetrahydro-PGI₁ compounds. These novel pharmacological agents are useful as smooth muscle stimulators.

27 Claims, No Drawings

2,2-DIFLUORO-TRANS-4,5,13,14-TETRAHYDRO-PGI₁ COMPOUNDS

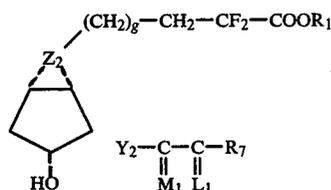
CROSS REFERENCE TO RELATED APPLICATION

The present application is a continuation-in-part application of Ser. No. 821,536, filed Aug. 3, 1977, now pending issuance as a U.S. Patent.

The present invention relates to prostacyclin analogs, for which the essential material constituting disclosure therefor is incorporated by reference here from Ser. No. 821,541, filed Aug. 3, 1977, now U.S. Pat. 4,109,082, issued Aug. 22, 1978.

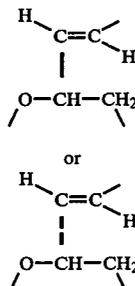
I claim:

1. A prostacyclin analog of the formula

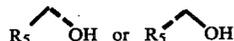


wherein Y₂ is $-\text{C}\equiv\text{C}-$.

wherein Z₂ is

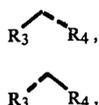


wherein g is the integer zero, one, or 2;
wherein M₁ is

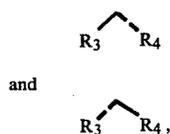


wherein R₅ is hydrogen or alkyl with one to 4 carbon atoms, inclusive;

wherein L₁ is



or a mixture of

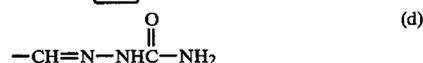
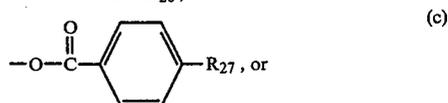


and



wherein R₃ and R₄ are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R₃ and R₄ is fluoro only when the other is hydrogen or fluoro;

wherein R₁ is hydrogen; alkyl of one to 12 carbon atoms, inclusive; cycloalkyl of 3 to 10 carbon atoms, inclusive; aralkyl of 7 to 12 carbon atoms, inclusive; phenyl; phenyl substituted with one, two or three chloro or alkyl of one to 3 carbon atoms; phenyl substituted in the para position by

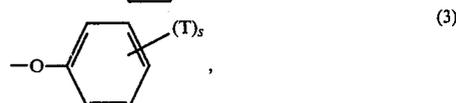
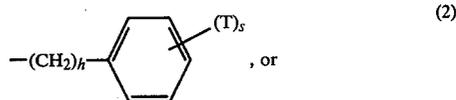


wherein R₂₅ is methyl, phenyl, acetamidophenyl, benzamidophenyl, or $-\text{NH}_2$; R₂₆ is methyl, phenyl, $-\text{NH}_2$, or methoxy; and R₂₇ is hydrogen or acetamido; phenacyl, i.e.,



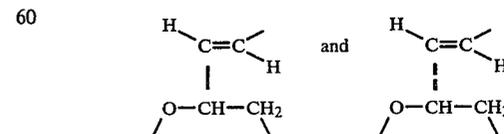
phenacyl substituted in the para position by chloro, bromo, phenyl, or benzamido; or a pharmacologically acceptable cation;

wherein R₇ is



wherein m is the integer one to 5, inclusive, h is the integer zero to 3, inclusive; s is the integer zero, one, 2, or 3, and T is chloro, fluoro, trifluoromethyl, alkyl of one to 3 carbon atoms, inclusive, or alkoxy of one to 3 carbon atoms, inclusive, with the proviso that not more than two T's are other than alkyl.

2. A prostacyclin analog according to claim 1, wherein Z₂ is a mixture of

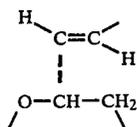


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3. 2,2-Difluoro(6RS)-trans-4,5,13,14-tetrahydro-PGI₁, a prostacyclin analog according to claim 2.

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4. A prostacyclin analog according to claim 1, wherein Z_2 is



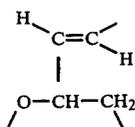
5. 2,2-Difluoro-trans-4,5,13,14-tetrahydro-6 α -PGI₁, a prostacyclin analog according to claim 4.

6. 2,2-Difluoro-15-methyl-trans-4,5,13,14-tetrahydro-6 α -PGI₁, a prostacyclin analog according to claim 4.

7. 2,2-Difluoro-16,16-dimethyl-trans-4,5,13,14-tetrahydro-6 α -PGI₁, a prostacyclin analog according to claim 4.

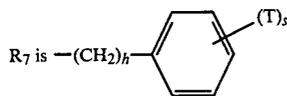
8. 2,2,16,16-Tetrafluoro-trans-4,5,13,14-tetrahydro-6 α -PGI₁, a prostacyclin analog according to claim 4.

9. A prostacyclin analog according to claim 1, wherein Z_2 is



10. A prostacyclin analog according to claim 9, wherein g is zero.

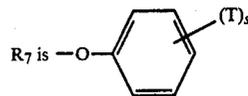
11. A prostacyclin analog according to claim 10, wherein



12. 2,2-Difluoro-17-phenyl-18,19,20-trinor-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 11.

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13. A prostacyclin analog according to claim 10, wherein



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14. 2,2-Difluoro-16-phenoxy-17,18,19,20-tetrahydro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 13.

15. A prostacyclin analog according to claim 10, wherein R_7 is $-(CH_2)_m-CH_3-$.

16. A prostacyclin analog according to claim 15, wherein R_5 is methyl.

17. 2,2-Difluoro-15-methyl-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 16.

18. A prostacyclin analog according to claim 15, wherein R_5 is hydrogen.

19. A prostacyclin analog according to claim 18, wherein at least one of R_3 and R_4 is fluoro.

20. 2,2,16,16-Tetrafluoro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 19.

21. A prostacyclin analog according to claim 18, wherein at least one of R_3 and R_4 is methyl.

22. 2,2-Difluoro-16,16-dimethyl-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 21.

23. A prostacyclin analog according to claim 18, wherein R_3 and R_4 are both hydrogen.

24. 2,2-Difluoro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, methyl ester, a prostacyclin analog according to claim 23.

25. 2,2-Difluoro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, tris(hydroxymethyl)amino methane salt, a prostacyclin analog according to claim 23.

26. 2,2-Difluoro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, adamantanamine salt, a prostacyclin analog according to claim 23.

27. 2,2-Difluoro-trans-4,5,13,14-tetrahydro-6 β -PGI₁, a prostacyclin analog according to claim 23.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

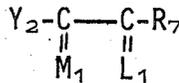
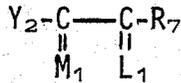
Patent No. 4,211,714 Dated 8 July 1980

Inventor(s) Herman W. Smith

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, lines 20-26, that portion of the formula reading

should read



Signed and Sealed this

Seventh Day of April 1981

[SEAL]

Attest:

RENE D. TEGMEYER

Attesting Officer

Acting Commissioner of Patents and Trademarks